GUIDANCE[1]

BUMETANIDE TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Bumetanide is a potent diuretic indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome. Bumetanide is contraindicated in anuria, hepatic coma, states of severe electrolyte depletion, and in patients hypersensitive to the drug.

The major site of action of bumetanide is the ascending limb of the loop of Henle where it inhibits the sodium-potassium-2 chloride absorptive pump (1).

Bumetanide tablets are currently marketed by Roche Laboratories as Bumex ® 0.5, 1.0, and 2.0 mg tablets. There is also a Bumex ® injection, 0.25 mg/ml, in 2 ml and 4 ml ampules (2). The usual daily dosing range for bumetanide is 0.5 - 2.0 mg.

B. Chemistry

Bumetanide, 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoic acid is a polar molecule at physiological pH, which

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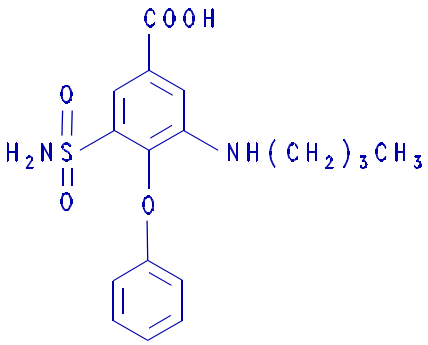
[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

promotes its urinary excretion (3). The structure of bumetanide is shown in the following formula:



BUMETANIDE

C. Pharmacokinetics

Bumetanide is reported to be readily absorbed from the gastrointestinal tract with a T_{max} of 0.5-2 hours (1,4,5,6), and a bioavailability of about 80-90% (1,4,5,6). Several pharmacokinetic studies have shown that bumetanide, administered orally, is eliminated rapidly in humans, with a half-life of between 1 and 2 hours (1,3,5,7). Plasma protein-binding is approximately 95% (6). Oral administration of bumetanide resulted in 36-60% recovery of the unchanged drug from urine (6,7,8,9). The volume of distribution (Vd) is approximately 0.2 L/kg (1). Following oral administration of bumetanide, the onset of diuresis occurs in 30 to 60 minutes (10,11). Peak activity is reached between 0.5 and 3 hours (10,11).

II. *IN VIVO* BIOEQUIVALENCE STUDIES[2]

A. Product Information

[2] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1) and also Office of Generic Drugs Policy and Procedure Guide #36-92, Submission of an "Investigational New Drug Application" to the Office of Generic Drugs, issued October 13, 1992.

1. FDA Designated Reference Product: Bumex [R] 2.0 mg tablet (Roche Laboratories)

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger .

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Type of Study Required

A single-dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions comparing equal doses of the test and reference products.

C. Recommended Protocol for Conducting a Single Dose Bioequivalence Study Under Fasting Conditions.

Objective: To compare the rate and extent of absorption of the generic bumetanide tablet with that of the reference product Bumex [R] 2.0 mg tablet (Roche) when given as equal labeled doses.

Design : The study design should be a single dose, two-treatment, two-period, two-sequence crossover with at least a three day washout period between Phase I and Phase II dosing. Equal numbers of subjects should be randomly assigned to the two possible dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names, titles and curriculum vitae of the medical and scientific/analytical directors.

Selection of Subjects: The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. Subjects should be healthy male volunteers aged 18 to 50 years and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical

examination, and clinical testing. Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the studies.

Procedure: Following an overnight fast of at least 10 hours, subjects should be administered a single dose (2.0 mg) of the test or reference product with 240 ml of water. The subjects should drink 240 ml of water at the following times: -2, -1, 0, 1, 2, 4, 6, 8, and 10 hours relative to dosing.

Restrictions: Study volunteers should observe the following restrictions:

a. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

b. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

c. Subjects should take no Rx medications beginning two weeks and no OTC medications beginning one week before drug administration and until after the study is completed.

Blood Sampling: Venous blood samples in a volume sufficient for sample analysis and anticoagulated as appropriate should be collected pre-dose (0 hours) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 5, 6, 8, and 12 hours post-dose. Plasma should be separated promptly, immediately frozen and stored at -20^{o} until assayed.

Urine Sampling: Urine may be collected over the following time intervals: -2 to 0, 0 to 1, 1 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, and 10 to 12 hours post-dosing. The urine volume and pH should be noted. One 50 ml aliquot should be stored refrigerated for possible analysis of sodium and potassium. A 15 ml sample should be stored frozen at -20 ^{o} for possible bumetanide assay.

Analytical Methods: High-performance liquid chromatographic methods have been reported for assaying bumetanide in human plasma (12-14) and urine (13-15).

Bumetanide should be assayed using a suitable method fully validated with respect to stability, sensitivity, specificity, linearity, recovery, accuracy and precision (both within and between days) (16). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curve and Q.C. chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data (Plasma): See Division of Bioequivalence Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design".

Diuretic Effects and Bumetanide Urinary Excretion Data :

Urine samples may be analyzed to determine the following parameters:

a. The mean rate of excretion of sodium, potassium, water and bumetanide for each collection period

b. The maximum excretion rate (excretion rate calculated for that time interval during which the rate is highest) for sodium, potassium, water and bumetanide

c. Time to maximum excretion rate for sodium, potassium, water and bumetanide

d. Cumulative excretion of sodium, potassium, water and bumetanide over all sampling time intervals

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations should be reported.

Retention of Samples: The laboratory conducting the bioequivalence testing should retain an appropriately

identified reserve sample of the test product and the reference standard used to perform the *in vivo* bioequivalence study(ies) for approval of the application. Each reserve sample should consist of at least 200 dosage units. For more information on retention of bioequivalence samples please refer to CFR 21,320.32

III. *IN VITRO* TESTING REQUIREMENTS

A. Dissolution Testing

Dissolution testing should be conducted on 12 dosage units of the test product versus 12 units of the reference product. The current official USP dissolution method should be followed and should be referenced by the sponsor. The following USP XXII method and tolerances are currently recommended for this product:

Apparatus:	Paddle
RPM:	50
Medium:	Water
Volume:	900 ml
Sampling Times:	10, 20, 30,and 45 minutes
Tolerance (Q):	NLT 85% in 30 minutes
Analytical:	Fluorescence at 450/350 nm (as per USP XXII) or other validated method

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

Lot numbers for both test and reference products must be the same as were used in the bioequivalence study.

The expiration date for the reference product should be submitted.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXII.

IV. WAIVER REQUIREMENTS

A. Waiver of *in vivo* bioequivalence study requirements for the 0.5 mg and 1.0 mg strengths of the generic product may be granted per 21 CFR 320.22(d)(2) provided both of the following conditions are met:

1. The 0.5 mg and 1.0 mg tablets are proportionally similar in both active and inactive ingredients to the 2.0 mg tablet for which *in vivo* bioequivalence to the reference 2.0 mg product has been demonstrated.

2. The 0.5 mg, 1.0 mg, and 2.0 mg tablets of the generic product meet the dissolution testing requirements.

VI. REFERENCES

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